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RESPONSE OF HEMATOPOIETIC SYSTEM TO X-RAYS

by

George M. Suter, M.D.

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RESPONSE OF HEMATOPOIETIC SYSTEM TO X-RAYS

By George M. Suter, M.D.

As you have heard in previous lectures, there is an effect of irradiation seen in almost every organ system.

There is apparently a gradation of sensitivity which appears to be somewhat proportional to the degree of primitiveness of the tissue in question. Thus, in the highly specialized tissue of the C. N. S. few effects are seen unless the exposure be relatively high and usually far in excess of a fatal dose. The peripheral blood, however, constantly replenishing itself from its bone marrow and lymphopoietic precursors, is very sensitive to both gamma and neutron radiation.

Interest in this subject in the past has been largely that of the X-ray therapist. At the present time a tremendous field has developed in atomic research on the part of those working with X radiation, cyclotron, radioisotopes, as well as those working directly in connection with the development of atomic energy both for military as well as civilian research purposes. Because of the sensitivity of the hemopoietic system and the relative availability of the peripheral blood for study, hematology has assumed foremost importance.

In the study of the peripheral blood numerous laboratory animals have been used. Studies of the effects on the peripheral blood can be divided into two types: that of animals acutely exposed and chronically exposed to whole-body radiation. Attempts have been made to compare species sensitivity of the various laboratory animals on various bases in order that some conclusions may be made about the effects on humans. On the basis of mortality studies the most sensitive species that we have studied appears to be the dog, with monkey, rat, and rabbit correspondingly less sensitive. We have found it difficult to draw such conclusions from the study of the blood of these animals (Figures 1, 2, and 3).

The site of injury with X radiation and neutron radiation appears to be directly in the blood-forming organs, the bone marrow, lymph nodes, and spleen. The peripheral blood shows only slight changes when isolated and radiated directly. Numerous investigators have found that different degrees of blood damage vary, depending upon the portion of the body that is exposed. These regional differences in the effectiveness of radiation may be explained by differences in the amount of blood or hemopoietic tissue included in the various fields of treatment. Perhaps other unknown factors are involved.

HEMATOLOGICAL EFFECTS OF ACUTE RADIATION

The peripheral blood counts of animals X radiated in large, single, whole-body doses show rather similar types of reactions without regard for species. For purposes of brevity, and because the different species do not show radical differences, we will confine our description to rats concerning the hematological effects of acute radiation.

In rats the graphs of the red blood count and of the hemoglobin show falls at 7 days in those groups radiated with from 300 and 500 r of total-body radiation. In doses above this there is an initial rise which is seen at about 3 days. The higher radiated groups then show a marked fall which is correspondingly greater with higher doses of radiation. This depressed phase continues for about 20 days after the treatment, following which there is a rise toward normal. Normal levels are attained 25

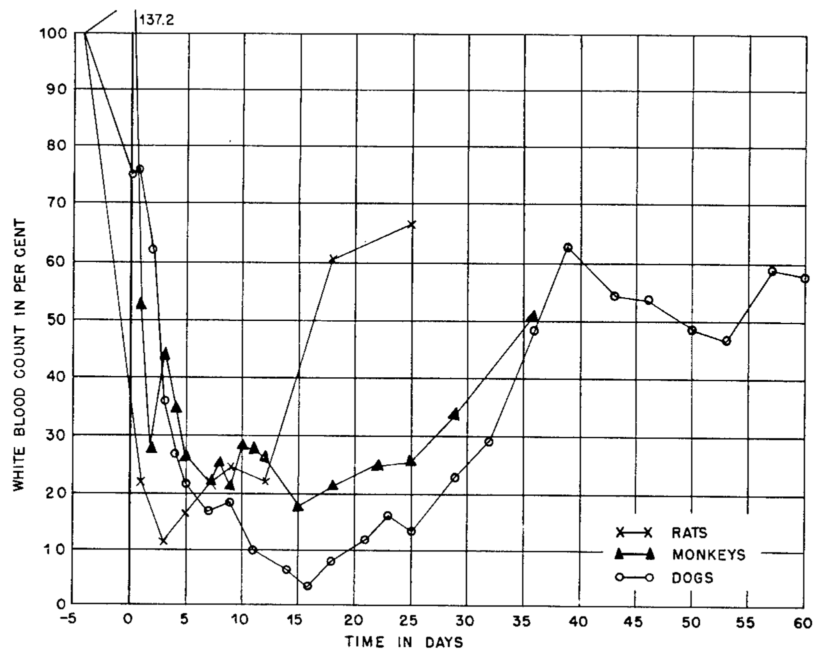

Figure 1. White blood count (300 r).

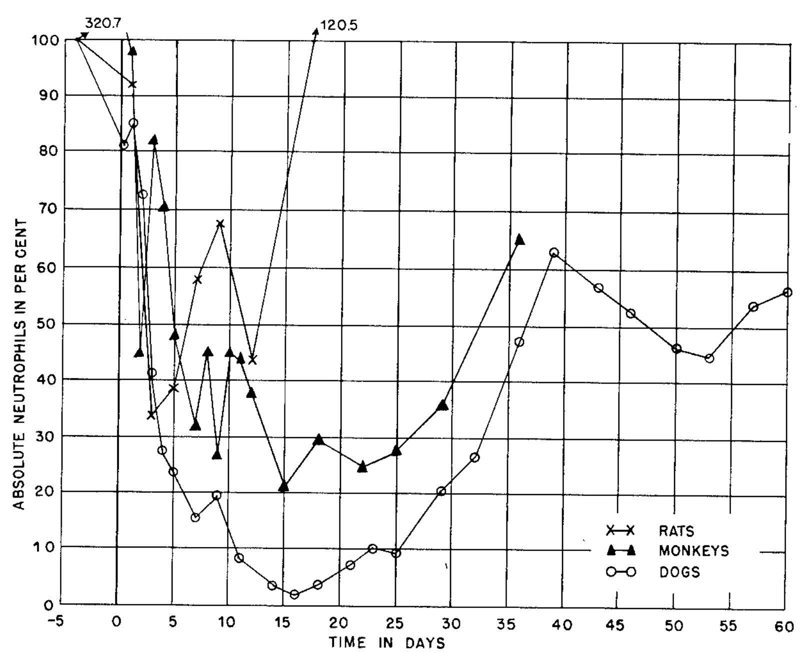

Figure 2. Absolute neutrophils (300 r).

days after radiation in the groups to 300 r and less. In the higher dosage groups the counts are low but still rising. The picture is not entirely clear for the surviving higher dosage groups. However, at 550 r, the LD_{50} for rats, it is known that the original levels are reached between 30 and 40 days after radiation (Figures 4 and 5).

The graph of the reticulocytes shows conclusive evidence of sensitivity to 100 r. Correspondingly greater effects are seen with higher doses of radiation, and in almost all instances when radiated with 500 r or greater the reticulocytes had fallen to zero at the end of 3 days. This low depressed phase continues for approximately 9 days in those radiated with 500 r and above. In those radiated with less there is a rapid return toward normal values. In the higher dosage levels, those which have been depressed for longer periods of time, the hemopoietic response to the anemia is very striking and the reticulocyte values rise to 2 to 3 times their original levels falling off after the compensation for anemia (Figure 6).

In the graph of the platelets, the platelets behave in a fashion somewhat similar to that of the red blood count and hemoglobin in that those levels exposed to 800 r and higher show an initial rise to about 3 days. As in the case of the red blood cells and hemoglobin this is probably due to hemoconcentration. This initial rise is followed by a very precipitous fall. The platelets appear to be sensitive to as little as 200 r of total-body radiation, showing a drop at this level after the 9th day after radiation. Twenty-five days after radiation almost normal levels have been reached in survivors exposed to 500 r or less (Figure 7).

Since in the normal rat the major component of the white blood count is the lymphocyte, any changes in the white count will be reflected in the lymphocytes.

In the graph of the absolute neutrophils the neutrophils show less sensitivity in the rat and the effects are less clear-out. However, it is safe to say that the dose of 200 r shows a fall at 3 days. Correspondingly greater falls at this time are seen with increasing levels of radiation. Doses of 500 r and above are practically indistinguishable for the first 3 days. Thereafter, an extremely low level is maintained until counts taken at 11 days in surviving animals show the beginning of a gradual rise which continues until counts taken at the 25th day show practically normal levels (Figure 8).

The lymphocytes are extremely sensitive to radiation and unquestionable falls are seen with as little as 25 r when counts are taken at 24 hours after radiation. Correspondingly greater falls are seen up through 200 r when counts are taken at 24 hours. With doses from 200 to 600 r it is impossible to differentiate the lymphocyte values at 24 hours. It should be noted that when counts are taken within a short time after radiation of doses in the range of the LD_{50} in rats, that a fall can be seen as early as 15 minutes after radiation (Figure 9). The lymphocyte values remain extremely low and counts taken 25 days after radiation still show less than normal values in groups exposed to 50 r or greater. In one experimental work in which relatively large numbers of animals were used, statistical evidence has been brought forth to indicate that the lymphocytes of rats are sensitive to as little as 5 r administered in a single dose (Figure 10).

Chronic studies were made for purposes of establishing tolerance both to X-ray and neutron radiation. The doses used were as shown in Table 1.

The various elements of the blood showed a drop with dosage indicated at week indicated. (Discuss each element for species designated in Table 1.)

There is a paradox to be pointed out at this point. You will recall that statistical evidence disclosed a fall in lymphocytes with as little as 5 r/day in rats. Here, with chronic radiation, no fall was seen using standard techniques of hematology until after 4 weeks of 10 r/day exposure had elapsed. This is due in part to the more exacting method used in the study of the group of rats exposed to 5 r at a single dose. Second the 10 r/day was administered at a slower rate than was the 5-r dose, and it has been established that the more rapid the exposure the greater is the effect. Third, the recuperative ability of the hemopoietic tissue is such that it may mask the effects of X radiation given chronically.

Table 1. Chart of chronic r/day and n/week.

Variable	Chronic r/day								Chronic n/ week					
	Dogs		Rabbits		Rats		Monkeys		Dogs		Rabbits		Rats	
	Dosage (r)	Time in weeks	Dosage (r)	Time in weeks	Dosage (r)	Time in weeks	Dosage (r)	Time in weeks	Dosage (n)	Time in weeks	Dosage (n)	Time in weeks	Dosage (n)	Time in weeks
RBC	10	16	10	16	10	32	------		10.2	$38\frac{1}{2}$	10.2	$32\frac{1}{2}$	10.2	6
Hemoglobin	10	16	10	28	10	48	------		10.2	$30\frac{1}{2}$	10.2	$32\frac{1}{2}$	10.2	11
Reticulocytes	3	16	--------		------		-------		-----		--------		------	
Platelets	6	8	10	12	------		-------		10.2	$26\frac{1}{2}$	--------		------	
WBC	6	16	10	4	10	4	10	1−2	10.2	$2\frac{1}{2}$	10.2	5	10.2	$1\frac{1}{2}$
Absolute Neutrophils	6	16	10	5	------		10	1−2	10.2	$2\frac{1}{2}$	10.2	$7\frac{1}{2}$	10.2	$2\frac{1}{2}$
Absolute lymphocytes	3	8	10	5	10	4	10	1−2	10.2	$4\frac{1}{2}$	10.2	$2\frac{1}{2}$	10.2	$1\frac{1}{2}$

(Chart showing per cent leukemias in both X radiation and neutron radiation when given chronically, Table 2)

Table 2.

	Leukemias
Controls	0%
0.1 r/day	1%
0.5 r/day	2%
1.0 r/day	3%
10.0 r/day	12%
Controls	0%
0.072 n/week	0%
0.36 n/week	0%
0.66 n/week	4%
10.2 n/week	16%

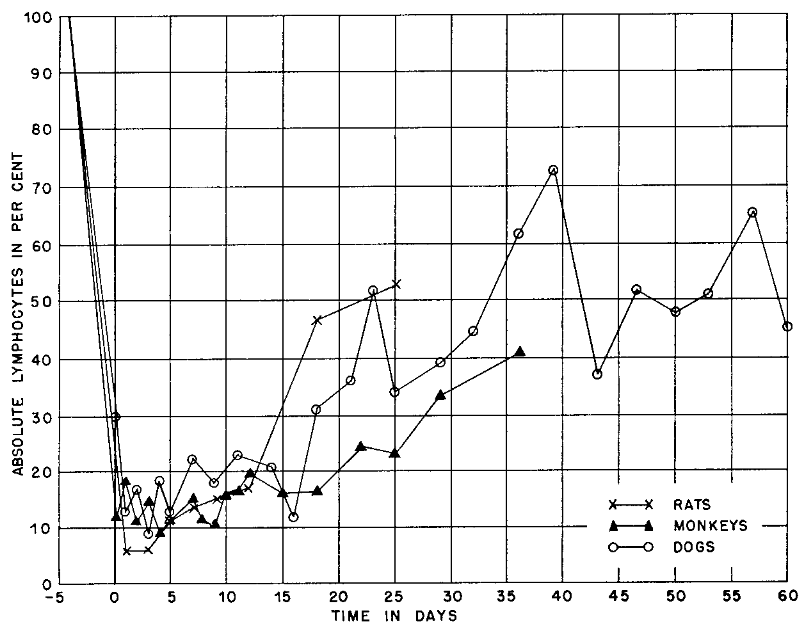

Figure 3. Absolute lymphocytes (300 r).

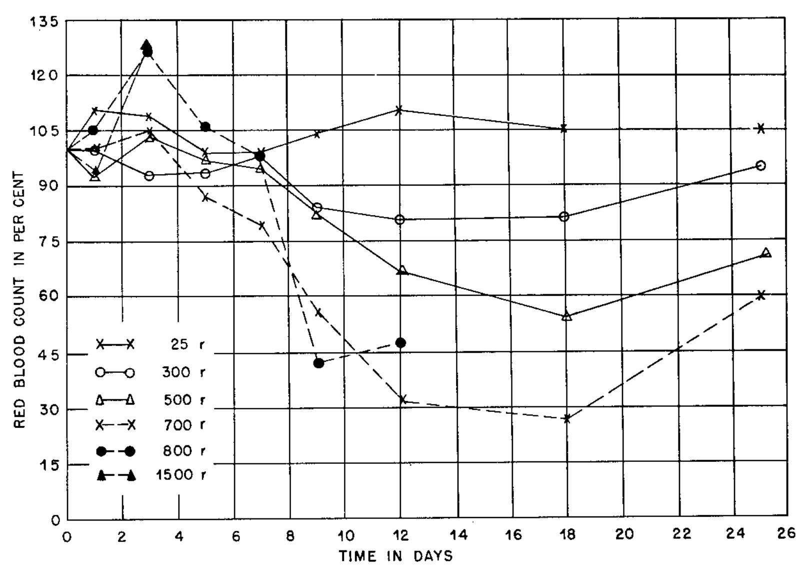

Figure 4. Red blood count.

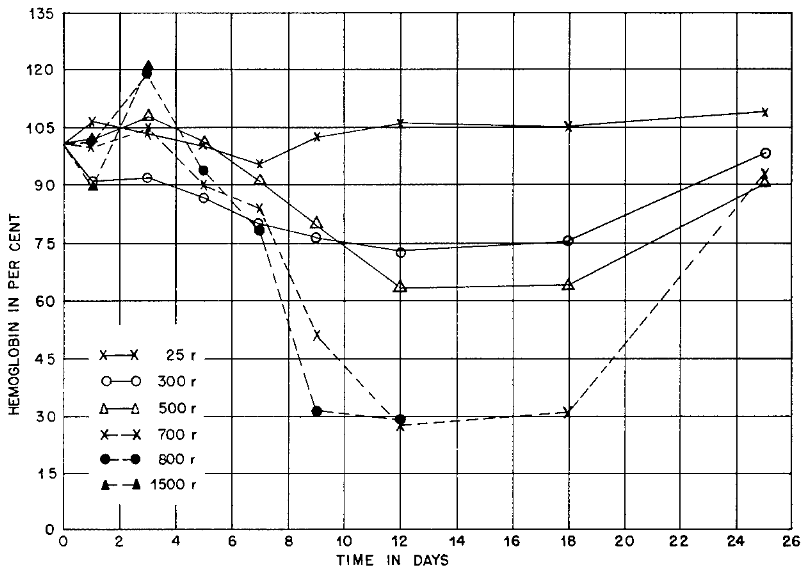

Figure 5. Hemoglobin.

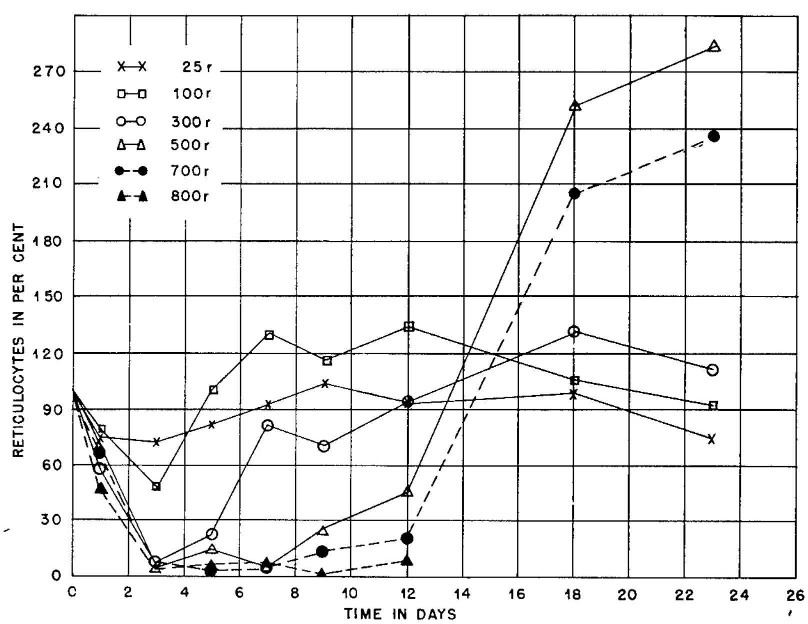

Figure 6. Reticulocytes.

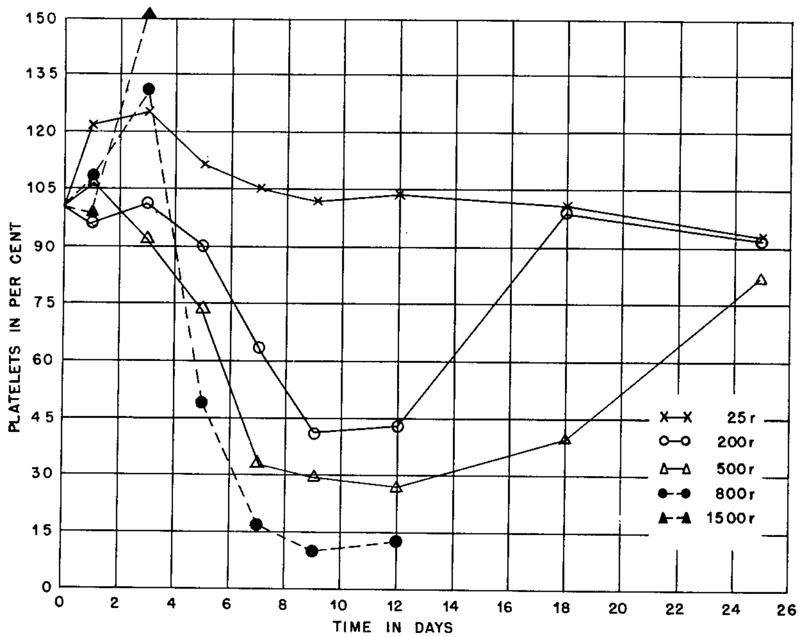

Figure 7. Platelets.

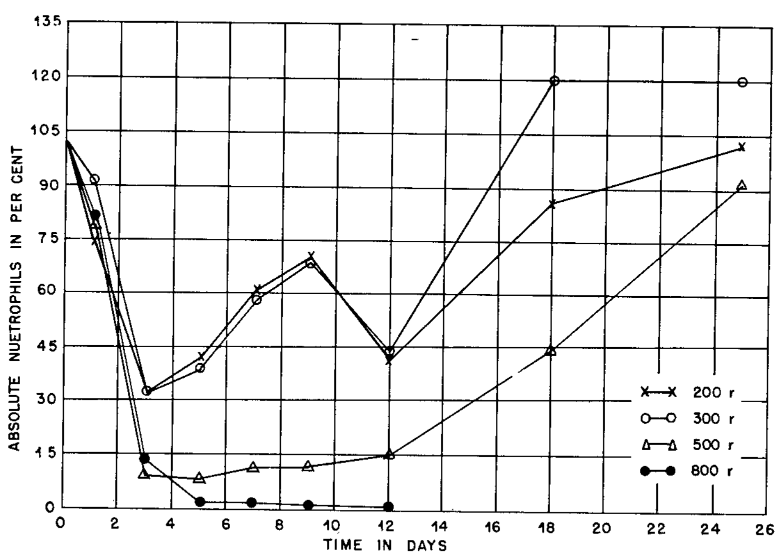

Figure 8. Absolute neutrophils.

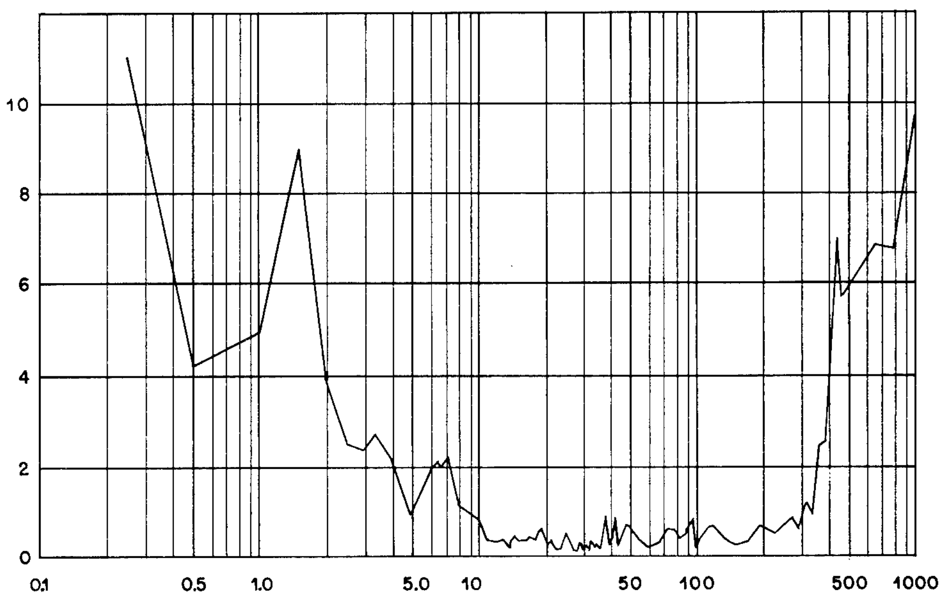

Figure 9. Absolute lymphocytes in thousands.

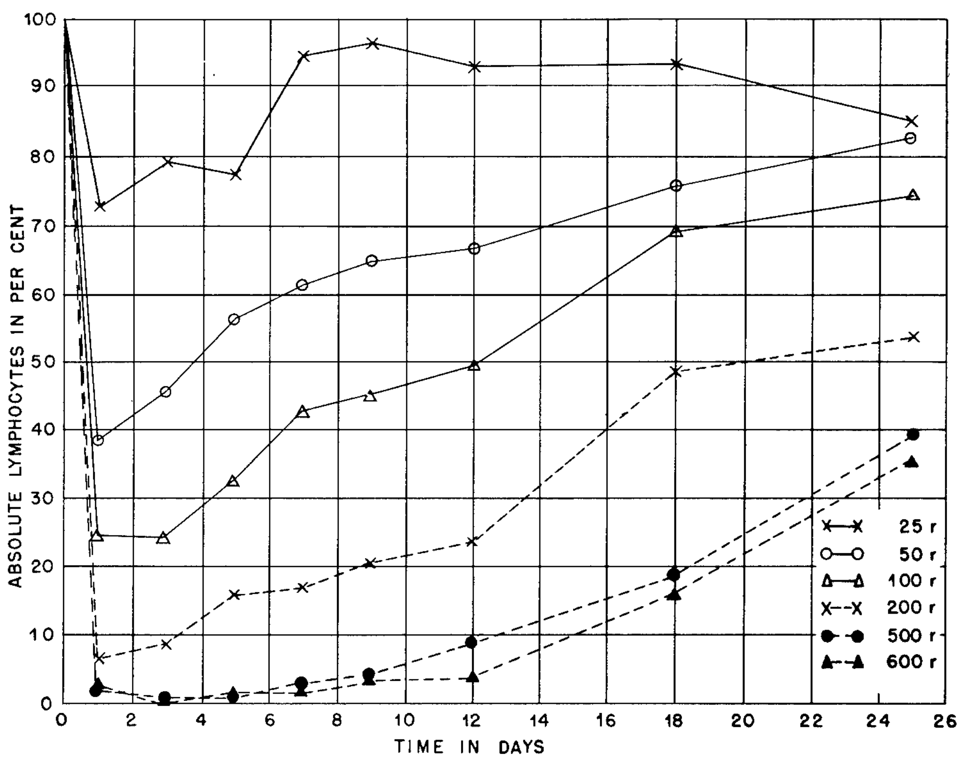

Figure 10. Absolute lymphocytes.